Association Between Erectile Function and Biomarkers of Subclinical Atherosclerosis: A Study Based on Middle-Aged Healthy Men from the General Population

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Key Words
Atherosclerosis • Erectile dysfunction • CRP • Obesity

Abstract

Introduction: Epidemiological studies suggest atherosclerosis as a common risk factor between cardiovascular diseases and erectile dysfunction (ED). We aimed to determine the association between erectile function and the biomarkers of subclinical atherosclerosis in 119 middle-aged healthy men from the general population. Methods: Erectile function was assessed using the International Index of Erectile Function-5 (IIEF-5). Serum levels of biomarkers of atherosclerosis: Apolipoprotein A, Apolipoprotein B, fibrinogen, and C-reactive protein (CRP) were measured. In addition, demographic data was collected. Results: The mean (SD) of age was 55 years (± 4.0). The prevalence of ED was 50%. There was a negative significant correlation between IIEF-5 and CRP levels ($r = -0.20$, $p = 0.02$), and BMI ($r = -0.20$, $p = 0.03$), respectively. No significant correlations between IIEF-5 and serum levels of Apolipoprotein A, Apolipoprotein B, and fibrinogen were found ($p > 0.05$). A positive significant correlation was found between BMI and fibrinogen ($r = 0.20$, $p = 0.01$), CRP ($r = 0.30$, $p = 0.001$). In a multivariate logistic regression model with IIEF-5 as the dependent variable, CRP was the only biomarker that predicted ED (odds ratio = 1.350; 95% CI: 1.044–1.754).

Conclusions: These results indicate that CRP is a biomarker of subclinical atherosclerosis associated with ED. This association seems to be linked to greater BMI among such men.

Introduction

Erectile dysfunction (ED) is defined as failure to obtain and maintain an erection sufficient for sexual activity or decreased erectile turgidity on 75% of sexual occasions and persisting for 6 months. It is also recommended that erectile disorder be defined independently of distress [1]. Based on large-scale prevalence studies, the prevalence of ED is estimated to be between 10% and 64% [2]. The prevalence of ED is age dependent with an estimated value of 8%; 11%; 15%; 22%; 30%; and 37% in men aged 20–29; 30–39; 40–49; 50–59; 60–69; and 70–75 years, respectively [3].

ED is a complex and multifactorial process including vascular, endocrinial, neurological, and psychological disorders. Indeed, the cause of organic ED often involves damage of the vascular endothelium due to atherosclerosis, which is a common link between cardiovascular dis-
eases (CVD) and ED [4, 5]. Damage of vascular endothelium results in reduction in the formation of nitric oxide thereby, decreasing maximal vasodilatation and blood flow, thus negatively impacting erectile function [6, 7].

Obesity has become one of the most urgent public health problems and poses a major threat to human health worldwide. The evidence presented in the literature indicates obesity as a major risk factor for metabolic syndrome, vascular disease, diabetes, hypertension, and endothelial dysfunction, all of which contribute to the pathophysiology of ED. Weight loss intervention was found to be helpful in maintaining erectile function in older overweight/obese diabetic men [8].

In the present study, we assessed the body mass index (BMI) of the men, and measured the serum levels of biomarkers of subclinical atherosclerosis including Apolipoprotein A (ApoA), Apolipoprotein B (ApoB), fibrinogen, and C-reactive protein (CRP). Our aim was to determine the association between these biomarkers and erectile function as assessed by the International Index of Erectile Function (IIEF-5) in a group of middle-aged healthy men from the general population.

Materials and Methods

This study was based on 119 middle-aged healthy men from the general population between January, 2006 and January, 2011. An invitation letter was sent to 1,601 men aged 40 to 60 years in the southern part of Sweden asking them to participate in a study about male sexual function and subclinical cardiovascular disease. Enclosed in the envelope were 2 questionnaires regarding their general medical health and sexual function. Men who were interested to take part of the study were asked to sign a written informed consent and submit it to the Department of Cardiology, Malmö University Hospital along with the completed questionnaires. A medical doctor then examined the completed questionnaires, and men who were found eligible were scheduled for an interview and thorough medical examination.

Exclusion criteria were past or present history of medical disease including diabetes, chronic inflammatory/infection diseases, psychological disease, or prescription of regular medications during the last 6 months prior to inclusion. Men outside the range of 40–60 years of age were not included.

Sexual function was assessed using the IIEF-5 with 5 domains (erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction). Each domain is scored on a 5-point scale with the lower results representing poorer sexual function. The total scores ranged from 5–25 points. Men were considered having normal erectile function with an IIEF-5 total score ranging from 22–25 points, and ED with IIEF-5 total score less than 22 points.

Data was also gathered on age, height, weight, marital status, smoking, snuff, alcohol consumption, and family history of cardiovascular diseases. Each man was asked to deliver a blood sample for analysis of biomarkers of subclinical atherosclerosis including ApoA, ApoB, fibrinogen, and CRP. The blood samples were taken between 07:00 and 10:00 am. The main outcome measures were erectile function as assessed by IIEF-5 and the biomarkers of subclinical atherosclerosis.

Statistical Analysis

Statistical analyses were done using the SPSS software, version 16 (SPSS, Inc; Chicago, IL). The correlations between erectile function as assessed by IIEF-5 and biomarkers of subclinical atherosclerosis (ApoA, ApoB, fibrinogen, and CRP), the age of subjects, BMI, and waist-to-hip ratio were performed using the Spearmen’s rank correlation coefficient test. Thereafter, the different variables were compared between men who were identified as having normal erectile function and those having ED using the Mann Whitney U test. Finally, using a multivariate logistic regression model, independent association was tested between the biomarkers of subclinical atherosclerosis (categorical variables), and IIEF-5 as dependent variable adjusted for known associations with ED (the age of subjects (46–50,51–55, 56–60 years); BMI (< 25, ≥ 25 kg/m²); waist-to-hip ratio (≤ 0.7, > 0.7); smoking (never, past, current); alcohol consumption (≤ 30 ml/week, > 30 ml/week); marital status (married, single); psychological disease, or prescription of regular medications during the last 6 months prior to inclusion). P-values below 0.05 were considered statistically significant.

Results

The questionnaire return rate was 16% (255/1,601). Of the 255 returned questionnaires, 108 were excluded (mainly due to prevalent cardiovascular disease such as hypertension). Of the remaining 147 men, 28 (19%) were further excluded, one with pathological echocardiogram, one with abnormal urological findings, 11 that did not

Table 1. Descriptive statistics of the study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (± SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 (± 4.0)</td>
<td>46–60</td>
</tr>
<tr>
<td>IIEF-5 (points)</td>
<td>20 (± 5.0)</td>
<td>8.0–25</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 (± 3.0)</td>
<td>20–38</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.0 (± 0.6)</td>
<td>0.85–1.2</td>
</tr>
<tr>
<td>ApoA (g/l)</td>
<td>1.4 (± 0.2)</td>
<td>0.9–1.9</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>1.0 (± 0.2)</td>
<td>0.3–1.6</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.5 (± 0.7)</td>
<td>1.4–6.6</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>2.0 (± 3.0)</td>
<td>0.2–16</td>
</tr>
</tbody>
</table>

Number = 119; IIEF-5 = International index of erectile function-5 items version; BMI = body mass index; ApoA = Apolipoprotein A; ApoB = Apolipoprotein B; CRP = C-reactive protein.
want to continue, and 15 that were excluded due to other
causes, resulting in 119 healthy men with full medical
examinations who were included in this study.

Descriptive statistics of the study population are sum-
mORIZED in table 1. The prevalence of ED was 50%. The
prevalence of know variables related to ED were as fol-
low: smoking (never 53%, past 25%, current 22%); snuff
(never 85%, past 2%, current 13%); marital status (mar-
ried 80%, single 20%); alcohol (yes 85%, no 15%); and
family history of CVD (yes 26%, no 74%).

We found a negative significant correlation between
IIEF-5 and CRP levels (r = -0.20, p = 0.02), and BMI (r =
-0.20, p = 0.02), respectively. On the other hand, no sig-
nificant correlations between IIEF-5 and serum levels of
ApoA, ApoB, and fibrinogen were found (p > 0.05). BMI
showed a positive significant correlation with ApoB, fi-
brinogen, and CRP levels (p < 0.05) (table 2).

Table 2. Correlation coefficients (r) between erectile function assessed by IIEF-5 and BMI, and biomarkers of atherosclerosis (ApoA, ApoB, fibrinogen, and CRP) in 119 healthy men from the general population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>IIEF-5 (r)</th>
<th>BMI (kg/m²) (r)</th>
<th>ApoA (g/l) (r)</th>
<th>ApoB (g/l) (r)</th>
<th>Fibrinogen (g/l) (r)</th>
<th>CRP (mg/l) (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIEF-5</td>
<td>–</td>
<td>-0.20*</td>
<td>0.10</td>
<td>0.10</td>
<td>-0.10</td>
<td>-0.20*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.20*</td>
<td>–</td>
<td>-0.40*</td>
<td>0.30*</td>
<td>0.20*</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*Indicate statistically significant correlations. Analysis was done using Pearson’s correlation coefficients rank. p < 0.05 is considered statistically significant.

Table 3. Comparison of age of subjects, BMI, waist-to-hip ratio, and biomarkers of atherosclerosis in regard to erectile function assessed by IIEF-5 score in 119 middle-aged healthy men from the general population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Erectile function (IIEF-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEF (N= 56)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (4.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (2.0)*</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.0 (0.6)*</td>
</tr>
<tr>
<td>ApoA (g/l)</td>
<td>1.4 (0.2)</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.5 (0.7)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.4 (2.0)*</td>
</tr>
</tbody>
</table>

Data are mean (± SD). NEF = normal erectile function. ED = erectile dysfunction. Analysis was done using Mann-Whitney U test. p < 0.05 is considered statistically significant.

Table 4. Independence of association between biomarker of atherosclerosis and EF (IIEF-5) obtained from a multivariate logistic regression model based on data from 119 middle-aged healthy men from the general population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>p</th>
<th>95% CI (Lower)</th>
<th>95% CI (Upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA (g/l)</td>
<td>0.308</td>
<td>0.399</td>
<td>0.020</td>
<td>4.768</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>0.267</td>
<td>0.247</td>
<td>0.029</td>
<td>2.501</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>0.439</td>
<td>0.133</td>
<td>0.150</td>
<td>1.286</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.350</td>
<td>0.022</td>
<td>1.044</td>
<td>1.745</td>
</tr>
</tbody>
</table>

Adjusted for the age of subjects (46–50, 51–55, 56–60 years); BMI (≤ 25, > 25 kg/m²), waist-to-hip ratio (≤ 1.0, > 1.0), smoking (never, past, current); snuff (never, past, current); alcohol (≤ 26.4, 26.5–115, 115.1–180, > 180 ml/week); marital status (married, single); and family history of CVD (yes, no). P < 0.05 is considered statistically significant.

Men with ED had significantly higher CRP levels, BMI, and waist-to-hip ratio as compared to men with normal erectile function (3.0 mg/l vs. 1.4 mg/l, p = 0.007); (27 kg/m² vs. 25 kg/m², p = 0.004); (1.0 vs. 0.98, p = 0.001), respectively. On the other hand, serum levels of ApoA, ApoB, and fibrinogen did not differ significantly between groups (p > 0.05) (table 3).

Finally, in a multivariate logistic regression model with erectile function as the dependent variable, the serum level of CRP was the only biomarker that predicted ED (odds ratio = 1.350; 95% CI: 1.044–1.754) (table 4).

Discussion

In this study based on 119 middle-aged healthy men from the general population, we found a negative significant correlation between IIEF-5 and CRP levels. Thus, men with ED had significantly higher CRP values as
compared to those having normal erectile function. CRP was the only biomarker of subclinical atherosclerosis that predicted ED, but BMI also showed a significant positive correlation with CRP and a significant negative correlation with ED. The correlations between IIEF-5 and BMI, and CRP may suggest that patients with severe ED have a greater BMI and higher inflammatory activation.

CRP is an important inflammatory biomarker of subclinical atherosclerosis and was demonstrated as an active molecule with relevance in the process of endothelial dysfunction. In this regard, it has been demonstrated in animal model that CRP leads to uncoupling of endothelial nitric oxide synthase (eNOS) and promotes oxidative stress [9, 10], and in the presence of aldosterone, leads to a hyperactivation of epithelial sodium channel (ENaC) [11]. ENOS is the main vascular endothelial nitric oxide synthetizer, so it was expected that the decrease in its activity would be followed by an impaired vasodilator capacity and also a hyperactivation of ENaC leading to a vascular stiffening and, thus, ED. In accordance, our study, as well as previous reports [12–16], demonstrated a negative significant association between CRP levels and ED. We were not able to find a significant correlation between IIEF-5 and fibrinogen in disagreement with previous results [17, 18]. This can be attributed to the differences in the number, age, and background characteristics of the subjects in different studies as well as to the method of classification of men regarding erectile function.

Obesity is a complex and multifactorial disease, has an inflammatory pattern and is associated with higher cardiometabolic risk. The parainflammation and the oxidative stress produced by an excess of adipose tissue can lead to endothelial dysfunction in different ways [19–21]. One of them is by increased serum levels of CRP, and indeed obesity has been proved to be linked to elevated CRP concentrations [20]. Moreover, in a randomized-controlled trial, it has been shown that obese men with ED who underwent a weight loss and increased their physical activity over a 2-year period had improvement in erectile function and endothelial function compared to matched controls [22]. In agreement, we found a positive significant correlation between obesity and levels of CRP.

Our study has some shortcomings; even though the men invited were randomly chosen from the general population, the participation rate in this study was only 16%, and one could question whether this group of men was representative for the general population of middle-aged Swedish men. Since no information was available for the men who chose not to reply to on the questionnaires, the characteristics of this group could not be compared to that of the included group of men. In addition, the sensitive nature of the ED topic in general may have reduced participation rates. However, we believe that the results are still valid and support the notion that there is no causal link between subclinical atherosclerosis and ED.

Our study has some clinical implications; it allows a better understanding of some of the pathophysiological aspects of ED among healthy men, and it indicates a role of obesity in the development of subclinical atherosclerosis and therefore ED. The nature of the present study, however, does not allow us to answer the question if whether these biomarkers can be used in the work up of young men with ED. In this regard, large case-control studies are recommended. Moreover, our study strongly supports the previous recommendation that modification of risk factors such as greater BMI may be beneficial for improving the erectile function.

In conclusion, we found a negative significant association between IIEF-5 and CRP levels in middle-aged healthy men. Among known biomarkers of subclinical atherosclerosis, CRP was the only biomarker that predicted ED. BMI showed a positive significant correlation with CRP and a negative significant correlation with IIEF-5. These results indicate that CRP is a biomarker of subclinical atherosclerosis associated with ED. This association seems to be linked to the greater BMI among such men.
References